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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,055	09/24/2004	Hiroaki Sagawa	1422-0644PUS1	9947

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EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
08/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,055	SAGAWA ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,12 and 14-35* is/are pending in the application.

4a) Of the above claim(s) *8 and 14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 10, 12, and 28-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 5/21/08 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/21/08 has been entered.

Claims 1-5, 10, 12, 28-31, and 33-35 have been amended.
Claim 36 has been cancelled.
Claims 1-8, 10, 12, and 14-35 are pending.

Claims 8 and 14-27 stand withdrawn from further consideration pursuant to 37 CFR 1.14209 as being drawn to a nonelected invention.

Claims 1-7, 10, 12, and 28-35 are under examination.

2. The rejection of the claims under 35 U.S.C. 112 second paragraph is withdrawn in view of Applicant's remarks and amendment to the claims.

3. The rejection the claims under 35 U.S.C. 112 first paragraph for lack of written description and enablement, as set forth in paragraphs 6 and 7 of the previous office action, is withdrawn in view of Applicant’s amendment to the claims.

4. Upon reconsideration, and in view of Applicant’s remarks, the rejection of claim 36 (the limitations of which are now incorporated into claim 1) under 112 first paragraph for new matter is withdrawn. The specification on page 35 discloses culturing PBMC, NK cells, umbilical cord blood mononuclear cells, hemopoietic stem cells, and blood component containing the cells for about 2-15 days to generate LAK cells. The specification further discloses in the next paragraph that the maintenance or expansion of cytotoxic cells can be performed in the same manner as mentioned above (i.e. by culturing said cells for 2-15 days).

5. The rejection of the claims under 35 U.S.C. 102 as being anticipated by Pollok et al. or under 35 U.S.C. 103 as being obvious over Ostergaard et al. are withdrawn in view of

Applicant's amendment. The references do not teach culturing for 2-15 days, as recited in the amended claims.

6. In view of the amendments to the claims, the obviousness type double patenting rejections are withdrawn. However, Applicant's arguments relevant to the new grounds of rejection will be addressed below.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-7, 10, 12, 28-30, and 33-35 stand rejected, under 35 U.S.C. 103(a) as being unpatentable over Mizobata et al., 1996, in view of U.S. Patent 5,198,423 (both of record).

As set forth previously, Mizobata et al. teach a method comprising expanding PBMC in the presence of anti-CD3 antibodies and human fibronectin (see page 1599 in particular). Mizobata et al. teach that the fibronectin is immobilized on a tissue culture plate (i.e. a "vessel", see page 1599 in particular). Mizobata et al. also teach that the cells are expanded at a concentration of 5×10^5 cells/ml (see page 1599 in particular). Mizobata et al. also teach that the expansion with fibronectin results in increased numbers of cytotoxic lymphocytes, some of which express CD8 (i.e. an increase in the number of CD8 positive cells, see page 1600 and Table IV, in particular). Mizobata et al. also teach that the fibronectin expanded cytotoxic lymphocytes have improved cytotoxic activity (see page 1600 in particular). Mizobata et al. also teach expanding the cytotoxic lymphocytes for 3 days (see page 1599 in particular). Mizobata et al. also teach that the fibronectin can result in increased expression of CD8 and IL-2 receptor (see Table IV, patient 8 had 1.4% CD8 positive cells with anti-CD3 alone, compared to 12% CD8 positive with CD3 and

fibronectin, and patient 5 on day 21 had 57% IL-2 receptor positive cells with anti-CD3 compared to 62% IL-2 receptor positive with anti-CD3 and fibronectin).

Mizobata et al. do not teach a fibronectin fragment comprising SEQ ID NO: 12, or immobilizing the fibronectin on a petri dish, flask, or bag.

The '423 patent teaches a biologically active recombinant fibronectin fragment comprising SEQ ID NO: 12 (see columns 3-4 in particular). The '423 patent also teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses (see column 1 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the recombinant fibronectin fragment taught by the '423 patent, for the human fibronectin in the method of preparing cytotoxic lymphocytes taught by Mizobata et al. The ordinary artisan at the time the invention was made would have been motivated to do so, since the '423 patent teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the recombinant fibronectin fragment, since the '423 patent teaches that the recombinant fibronectin is a biologically fragment. Additionally, it would have been obvious to culture the cytotoxic lymphocytes in a petri dish, a flask, or a bag, since these are all well known and routine vessels used for performing tissue culture.

Applicant's arguments filed 4/21/08 have been fully considered, but they are not persuasive.

Applicant argues that Mizobata et al. do not teach culturing blood cell components or PBMCS with fibronectin, IL-2, and anti-CD3, as recited in the instant claims. Rather, Applicant argues, Mizobata et al. teach culturing lymphocytes having an antigen specificity to tumor cells, which is artificially induced by placing them in the presence of tumor cells.

Mizobata et al. teach culturing a population of peripheral blood mononuclear cells (PBMCs) with tumor cells to induce cytotoxic T lymphocytes, followed by stimulating said cell population with IL-2, anti-CD3, and fibronectin. The fact that the method of Mizobata et al. comprises an extra step (i.e. first stimulating the PBMCs with tumor cells) is not relevant, since the instant claims are drawn to a method for expanding cytotoxic lymphocytes "comprising" culturing PBMCs with fibronectin. Mizobata et al. teach contacting tumor antigen stimulated PBMCs with fibronectin, IL-2, and anti-CD3. Furthermore, even if the cells of Mizobata et al. consist solely of "antigen specific lymphocytes" as asserted by Applicant, said lymphocytes originated from the blood, and can be considered a "peripheral blood mononuclear cell", as recited in the instant claims.

9. The following are new grounds of objection and rejection

10. Claim 29 is objected to because of the following informalities: The claim recites a method for increasing the number of CD8-positive cells "in a cytotoxic lymphocytes". The phrase is not grammatically correct. Appropriate correction is required.

11. Claims 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mizobata et al., 1996 and U.S. Patent 5,198,423, as applied to claims 1-7, 10, 12, 28-30, and 33-35 above, and further in view of Chen et al., 1994 (of record).

The combined teachings of Mizobata et al. and the '423 patent are described above.

They do not teach transducing a foreign gene into the cytotoxic lymphocytes.

Chen et al. teach that retroviral transduction of cytotoxic T cells with PKC allows long term growth of the cells in vitro with maintenance of cytolytic function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells (see pages 3634-3635, in particular).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to further transduce the cytotoxic lymphocytes made by the method of Mizobata et al. and the '423 patent, with a retrovirus encoding PKC, as taught by Chen et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so, and have a reasonable expectation of success, since Chen et al. teach that retroviral transduction of cytotoxic T cells with PKC allows long term growth of the cells in vitro with maintenance of cytolytic function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells.

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not

identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-7, 10, 12, and 28-35 are provisionally rejected, on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 8, 15-16, 30, 32, and 34 of copending Application No. 10/486,512, in view of Mizobata et al. and Chen et al., 1994.

The '512 application claims a method for inducing cytotoxic T cells, a method for maintaining cytotoxic T cells, and a method for expanding cytotoxic T cells comprising incubating peripheral blood mononuclear cells with fibronectin and anti-CD3. The '512 application further claims that the fibronectin can be SEQ ID NO: 6, which is identical to SEQ ID NO:12 of the instant application. Additionally, it would have been obvious to further expand the cells with IL-2, since Mizobata et al. teaches that IL-2 induces proliferation of cytotoxic T cells (see Fig. 1 in particular). Furthermore, the limitations of the instant claims where the fibronectin is immobilized on a substrate, wherein the concentration of cells is between 1 cell/ml to 5 x 10^5 cells per ml, and wherein culturing is performed for 2-15 days represent obvious variations of the method claimed in the '512 application (see for example, Mizobata et al.) and do not render the instant claims patentably distinct. Moreover, it would have been obvious to transduce the cytotoxic T lymphocyte with a foreign gene, since Chen teaches

that retroviral transduction with PKC allows long term growth of cytotoxic T cells in vitro.

This is a provisional obviousness-type double patenting rejection.

Applicant's request that the provisional obviousness-type double patenting rejections be reconsidered at the time of allowance is acknowledged.

14. Claims 1-7, 10, 12, and 28-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 20-21 of copending Application No. 10/568,745, in view of Mizobata et al.

The '745 application claims a method for preparing a cytotoxic lymphocyte comprising the step of carrying out at least one step selected from induction, maintenance, and expansion of a cytotoxic lymphocyte in the presence of fibronectin or a fragment thereof. The '745 application further claims that the fibronectin fragment comprises SEQ ID NO: 13, which is the same as SEQ ID NO: 12 of the instant application. The '745 application also claims that the fibronectin is immobilized on a substrate and that the concentration of cells is between 1 cell/ml to 5 x 10^5 cells per ml. The '745 application also claims that the lymphocytes can be transfected with a foreign gene using a retrovirus, adenonvirus, or simian virus. Additionally, it would be obvious to further expand the cells with IL-2 and anti-CD3, since Mizobata et al. teach that IL-2 and anti-CD3 induce proliferation of cytotoxic lymphocytes (see Fig. 1 in particular). Additionally, it would have been obvious to use PBMC as the source of the cytotoxic lymphocytes in the method claimed in the '745 application, since Mizobata et al. teach that cytotoxic lymphocytes can be derived from PBMC.

This is a provisional obviousness-type double patenting rejection.

Claim 1-7, 10, 12, and 28-35 are directed to an invention not patentably distinct from claims 1-15 and 20-21 of commonly assigned application 10/568,745. Specifically, the inventions are not patentably distinct for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300).

Commonly assigned application 10/568,745, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Applicant's request that the provisional obviousness-type double patenting rejections be reconsidered at the time of allowance is acknowledged.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 6am - 2pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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